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EXAMINER	
ROBINSON, HOPE A	

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 09/10/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/994,573	SEKI ET AL.	
	Examiner	Art Unit	
	Hope A. Robinson	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 June 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-7 and 10-23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-7 and 10-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2/25/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's response to the Office Action mailed August 20, 2003 on June 18, 2004 is acknowledged.

2. Claims 2 and 8-9 have been canceled. Claims 15-23 have been added. Claims 1, 3-7, 10-14 have been amended. Claims 1, 3-7 and 10-23 are pending and are under examination.

3. The rejections of record under 35 U.S.C. 112, first and second paragraphs have been maintained, however, the rejections have been amended in view of the amendments made to the claims.

4. The following grounds of objection/rejection are or remain applicable:

5. The Information Disclosure Statement filed February 25, 2004 has been considered, a copy of the 1449 is attached.

Specification

6. The specification is objected to because trademarks are disclosed throughout the instant specification and not all of them are capitalized or accompanied by the generic terminology. The use of the trademarks such as FUJI™ , PROMEGA ™, for example,

have been noted in this application (see pages 13-14). It should be capitalized wherever it appears and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner, which might adversely affect their validity as trademarks.

Correction is required.

Claim Objection

7. Claims 10, 16, 18 and 21 are objected to because of the following informalities:

Claim 16 is objected to because the claim does not further limit claim 15.

Claim 18 is objected to for the recitation of *E.coli.* instead of the spelled out meaning (see also claims 10 and 21). Note also the extraneous period following "coli". Correction is required.

Claim Rejections - 35 U.S.C. § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1-7 and 10-23 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as

to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 1, for example, is directed to a method of producing a soluble protein domain comprising (a) expressing at least two nucleotide sequences each encoding a fusion protein comprised of a fragment of a starting protein and a protein exhibiting a function, (b) selecting a fusion protein exhibiting said function from among the proteins synthesized in step (a), as comprising a fragment of said starting protein that is a soluble domain, and synthesizing the soluble domain included in the fusion protein selected in step (b) in a cell free system. The claimed method as amended is not adequately described, as steps (a) and (b) do not lead to step (c) and step (c) does not achieve the preamble of the claim. The claim requires any protein exhibiting function fused to a fragment of a starting protein (any protein) and there is no requirement that the DNAs in step (a) are different, thus, the encoded proteins could be the same. In addition, step (b) appears to already contain the soluble protein domain that is suppose to be synthesized in step (c). The method is missing a recovery step to indicate that the soluble protein is obtained because the method as written only obtains a fusion protein that exhibits some function and that may contain a soluble domain. Thus, the method steps set forth do not demonstrate possession of the a soluble protein domain as there is no step to cleave and isolate/recover said domain to indicate the protein domain is in hand.

Claim 3 as amended requires a protein exhibiting a function selected from the group consisting of an enzyme, a binding protein, a luminescent protein, a fluorescent

protein and functional portions thereof, thus the claim encompasses a genus of proteins (see also claims 4, 15, 19 and 20). The claims are directed to "a functional portion thereof" and "variant thereof" and the instant specification fails to provide any additional representative species of the claimed genus to show that applicant was in possession of the claimed genus. A representative number of species means that the species, which are adequately described, are representative of the entire genus. The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, disclosure of drawings, or by disclosure of relevant identifying characteristics, for example, structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. The claimed invention encompasses DNAs encoding fusion proteins that comprise a fragment of a starting protein and a protein exhibiting a function and the protein fragment once fused with the protein exhibiting a function may result in a protein that has the same function, a different function or no function, hence the claimed invention lacks adequate written description.

Additionally, the method as claimed in "claim 5 requires selecting a clone which exhibits said function", however, the method of claim 1 does not describe a clone having function being selected, the method of claim 1 describes fusing a starting protein to a protein exhibiting function. Note also that claim 10 may not result in a soluble protein.

Step (a) begins with providing an expression vector, which expresses a fusion protein with a GFP, thus, the protein in step (a) may already be soluble. Claim 10 recites a method for producing a soluble protein domain comprising method steps (a-f), however, these steps may not result in the production of a soluble protein. Step (a) begins with constructing an expression vector, which expresses a fusion protein with a GFP thus, the protein in step (a) may already be soluble. In addition, steps (b-e) comprise, preparing two or more DNA fragments for partial digestion, transforming *E. coli* with each DNA, isolating a transformed clone and recovering the DNA from the isolated transformed clone and then synthesizing the soluble protein domain. Essential method steps are omitted between items (b) through (e), thus, the method as claimed does not lead to the production of a soluble protein domain. In addition, the claimed step (e) does not guarantee that one of skill in the art performing this would be left with a soluble protein to be able to synthesize the soluble protein domain in a cell free system as required by step (f). Note that what is recovered is the DNA, then the protein is synthesized but there is no indication of cleavage and recovery of the protein. Thus, the method steps recited in claim 10 are not adequately described and do not necessarily result in the desired product, especially since the method has no recovery/isolation step.

Note that claim 11 is directed to a method similar to claim 10, however, step (a) selects a fusion protein that exhibits a function characteristic of a functional protein from a plurality of fusion proteins.... The characteristics of said protein is not set forth, yet the claim recites "a function characteristic of a functional protein". The specification does not provide any special features of the fusion partners to adequately describe the

invention as claimed in claim 11. Note also that the method of claim 11 does not have the desired end point as step (b) results in a fusion protein not a soluble protein domain (see also claims 13, 15 and 21 where the end result does not match the preamble).

Therefore for these reasons, the claimed invention lacks adequate written description and one of skill in the art could not reasonably conclude that applicant had possession of the claimed invention at the time of filing.

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 1, 3-7 and 10-23 are rejected under 112, second paragraph as failing to distinctly point out the subject matter applicant regards as his invention.

(A) Claims 1, 10 and 13 are incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: between step (a) and (b) and step (c) of claim 1 for example, as the preamble is directed to producing a soluble protein domain, however, step (c) results in a fusion protein as the soluble protein domain has not been cleaved and isolated/recovered in this step. In addition, it is unclear how a partially digested DNA encoding a protein leads to the expression of a fusion protein and how selecting a fusion protein leads to synthesizing a soluble protein domain, see for example claims 10 and 13. It is noted that on page 7 of the instant specification, it is stated that "it is essential that the DNA fragments are properly ligated to a gene coding for a functional protein". However, the

limitations of the specification cannot be read into the claims, and the claims do not recite all the necessary steps, thus, the methods as claimed omit essential method steps (see also claims 15 and 21).

In addition, claim 1 as amended lacks antecedent basis for "said starting protein that is a soluble domain" because the preamble recites a method to produce a soluble protein domain comprising a fragment of a starting protein". Note also that step (c) lacks antecedent basis for "synthesizing the soluble domain" because according to step (b) the soluble domain is comprised in step (a).

The claim also lacks antecedent basis for "said function" in step (b) as step (a) recites "a function". The dependent claims hereto are also included in this rejection.

(B) Claim 3 is indefinite, as the claim has improper Markush language; a Markush claim listing can be " A, B and C" or "A, B or C". The claim in lines 3-4 list the following, "an enzyme, a binding protein, a luminescent protein and a fluorescent protein and functional portions thereof".

(C) Amended claim 5 lacks antecedent basis for "a clone which exhibits said function" as the independent claims recites "a fusion protein exhibiting function" (see also claim 14). The dependent claims are included.

(D) Amended claim 10, is indefinite because the claim is missing a transitional phrase following "with" in line two. (see "a first protein with a second protein). The claim is further indefinite for the recitation of "selecting a fusion protein that exhibits a function characteristic of a functional protein", because it is unclear what characteristics are

being referred to, since most proteins have different characteristics (see also claim 13 (d)). The dependent claims hereto are also included.

(E) Claim 11 is confusing because the claim recites "a second protein which is a candidate soluble domain, wherein in the selected protein said second protein is a soluble domain" as this phrase appears to be redundant.

(F) Claim 13 lacks proper antecedent basis for "the function" in step (d) as step (a) recites "functional protein".

(G) Claim 15 lacks antecedent basis for "fragment" in step (a) as the preamble recites "a portion of" (see also clam 21). For clarity the phrase "each said fusion protein" should be replaced with "each of said fusion protein". The claim is also confusing for the recitation of " a portion of a starting protein"; "a protein identified as said soluble domain"; "each said fusion protein comprising a functional portion and a fragment of said starting protein" because it is unclear if the starting protein is the protein with the soluble domain or the functional portion of the fusion. The claim is further indefinite as the preamble is directed to a method to synthesize a soluble domain, which is the same as a method to produce a soluble domain, step (c) is directed to identifying as a soluble domain fragments of said protein contained in the fusion.... Clearly, the preamble is not achieved (see also claim 21). The dependent claims are also included in this rejection.

(H) Claim 21 lacks antecedent basis for "soluble protein domain" in step (c) as the preamble recites "soluble domain".

Claim Rejections - 35 U.S.C. § 103

The following is a quotation of 35 U.S.C. 103 (a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains.

10. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103 (a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103 (c) and potential 35 U.S.C. 102 (f) or (g) prior art under 35 U.S.C. 103 (a).

11. Claims 1, 3-7, 10-16 and 19-20 are rejected under 35 U.S.C. 103(a) as obvious over Chien et al. (PNAS, vol. 88, pages 9578-9582, November 1991) in view of Waldo et al. (Nature Biotechnology, vol. 17, pages 691-695, 1999). The art has been broadly applied to the recited methods although essential method steps are missing to demonstrate that the present method steps are obvious.

The disclosure state that a partially digested DNA means using a DNA decomposing enzyme treatment such as Dnase I, various Restriction enzymes, Bal31, Exonuclease III and other generally known enzymes. (pages 6-7).

Chien et al. teaches cutting Gal4 into fragments with restriction enzymes (DNA decomposing enzyme, claim 10) and the expression of a fusion protein (claims 1 and 12-13), the fusion partner being lacZ, which has expressed function and is luminescent (claims 3 and 19), see page 9579. In addition, the reference teaches transforming *E. coli* with the DNA (claims 5, 6 and 14). Further, the instant specification states on page 8 that "solubility of proteins coded on the DNA fragments can be predicted. As a concrete example, they can be prepared using the reporter genes mentioned below, for example, a beta-galactosidase gene derived from *E. coli* (lac Z)", which functions as admitted prior art. In-so-far-as Chien et al. do not teach GFP, Waldo et al. teach GFP fusion proteins (claims 4, 11 and 20) for the formation of folding robustness to improve soluble expression in *E. coli*. The Chien et al. and Waldo et al. references do not recite the use of a cell-free expression system for the production of a soluble protein domain, as Chien et al. and Waldo et al. use cell based systems. However, in vitro translation systems such as reticulocyte lysate or wheat germ lysates for the production of polypeptides in a cell free system are well known in the art (see also pages 10-11 of the specification where it is stated that these are generally known). Use of such systems have the advantage over cell based systems that one has control over the particular proteins expressed within the system such that production of undesired enzymes, such as glycosyltransferases which would produce heterogeneity in an oligosaccharide

synthesis) can be eliminated. As such it would have been obvious to one of skill in the art that the cell based system as disclosed by the references can be substituted for the cell free systems recited in the claims with a reasonable expectation of success (claims 7 and 16).

Therefore, it would have been obvious to one of ordinary skill in the art to obtain the invention as a whole because Chien et al. partially digests DNA with restriction enzymes, and expresses a fusion protein (with function) and Waldo et al. teach folding robustness using GFP fusions and partially digested DNA via restriction enzymes. One of ordinary skill in the art would be motivated to combine the teachings of the references because it is known in the art that GFP is a reporter of gene regulation and Waldo et al. teach the advantages of using GFP to obtain soluble domains. Therefore, at the time of filing the claimed invention was obvious to make and use.

12. Claims 10-14 and 21-22 are rejected under 35 U.S.C. 103 (a) as being unpatentable over Waldo et al.(Nature Biotechnology, vol. 17, pages 691-695, 1999). The art has been broadly applied to the recited methods although essential method steps are missing to demonstrate that the present method steps are obvious.

Waldo et al. teach DNA encoding a protein of function that is subjected to DNA shuffling which is equivalent to a partial digest (claim 12) as a restriction enzyme is used to cut the DNA into fragments (claim 10, page 692). The reference also teaches the construction of a folding reporter vector (claim 13) in which a test protein is expressed as an N-terminal fusion with GFP in *E. coli* (claims 10 and 21-22, page 691). Waldo et

al. teach that a plurality of proteins were used, a panel of 20 test proteins (abstract, claim 11). The reference also teaches testing to ensure that there is no loss of function (claim 13). The reference teaches the production of a soluble protein domain, however, does not teach a cell free system. The Waldo et al. reference does not recite the use of a cell-free expression system for the production of a soluble protein domain, while Waldo et al. use cell based systems. However, in vitro translation systems such as reticulocyte lysate or wheat germ lysates for the production of polypeptides in a cell free system are well known in the art (see also pages 10-11 of the specification where it is stated that these are generally known). Use of such systems have the advantage over cell based systems that one has control over the particular proteins expressed within the system such that production of undesired enzymes, such as glycosyltransferases which would produce heterogeneity in an oligosaccharide synthesis) can be eliminated. As such it would have been obvious to one of skill in the art that the cell based system as disclosed by the references can be substituted for the cell free systems recited in the claims with a reasonable expectation of success (claim 7).

Therefore, it would have been obvious to one of ordinary skill in the art to obtain the invention as a whole because Waldo et al. partially digests DNA with restriction enzymes, expresses a fusion protein (with function) and teach folding robustness using GFP fusions. Additionally, Waldo et al. teach the advantages of using GFP to obtain soluble domains. Therefore, at the time of filing the claimed invention was *prima facie* obvious.

13. Claims 15-16, 19-22 are rejected under 35 U.S.C. 103 (a) as being unpatentable over Kawasaki et al.(Biochemical and Biophysical Research Communications, vol. 280, issue 3, pages 842-844, January 26, 2001). The art has been broadly applied to the recited methods although essential method steps are missing to demonstrate that the present method steps are obvious.

Kawasaki et al. teach a method to synthesize/produce a soluble domain by examining all possible protein fragments using GFP as a fusion partner and to monitor the solubilities (claims 15 and 21). In the Kawasaki et al. method a GFP reporter vector was constructed, digested and the fragments were eluted and ligated and used to transform *E. coli*. The transformed cells were plated and GFP fusion proteins were expressed. The expressed protein was purified. The reference teach that the solubility of the translation products were monitored by the fluorescence of the transformed *E. coli* colonies on plates and four soluble domains were cloned from Vav proteins using this method (see claims 19-20, 22 and pages 842-843 of the reference). The reference teaches the production of a soluble protein domain, however, does not explicitly teach a cell free system. The Kawasaki et al. reference does not recite the use of a cell-free expression system for the production of a soluble protein domain. However, *in vitro* translation systems such as reticulocyte lysate or wheat germ lysates for the production of polypeptides in a cell free system are well known in the art (see also pages 10-11 of the specification where it is stated that these are generally known). Use of such systems have the advantage over cell based systems that one has control over the particular proteins expressed within the system such that production of undesired

enzymes, such as glycosyltransferases which would produce heterogeneity in an oligosaccharide synthesis) can be eliminated. As such it would have been obvious to one of skill in the art that the cell based system as disclosed by the reference can be substituted for the cell free systems recited in the claims with a reasonable expectation of success (claim 16).

Therefore, it would have been obvious to one of ordinary skill in the art to obtain the invention as a whole because Kawasaki et al. teach the production of soluble domains using GFP fusions expressed in *E. coli* which emits fluorescence and that their method is most useful in searching soluble variants (see page 844). Therefore, at the time of filing the claimed invention was within the skill of the art and *prima facie* obvious.

14. Applicant's response filed June 18, 2004 has been considered. Based on the amendments made to the claims the rejections of record have been amended to incorporate the modifications in the claims as well as new grounds of rejections have been instituted for the amendatory language and the newly submitted claims, for the reasons stated above.

Regarding the rejection under 35 U.S.C. 112, first paragraph, written description applicant on page 10 state that it is unclear what the particular defects are. Note that the rejection remains for the reasons stated above. The issue raised in the rejection is two fold, applicant has not adequately described the claimed invention because method steps are missing, for example a step to cleave and recovery the protein as the methods claimed either result in a fusion protein or a DNA. An end step is necessary to

demonstrate possession of the claimed soluble protein domain. In addition, the claims encompass variants, fragments or portions of proteins not adequately described, yet is expected to have function or function characteristic of a functional protein. The claims encompass a genus of proteins for which a representative number of species is not described and for which the instant specification does not demonstrate possession.

Applicant state that there are multiple ways the steps of the method could be performed, however, this argument is not persuasive with regard to the claimed invention missing essential method steps, as the description given in the instant specification and recited in the claim as to how to practice the claimed method is the only way of interest. The claims are directed to methods of synthesizing or producing a soluble protein domain, hence applicant needs to provide the necessary method steps to allow a skilled artisan to achieve the objective of the claimed method. Applicant argues that the amendments to the claims have clarified the methods, however, as stated above the methods are still lacking essential method steps. The specification provides very little description as to what GFP, from what source, what variant, does the variant have function, does the fusion product retain function, for example, yet the methods are directed to fusing a protein with function and identifying the function, for example. Arguably, once a portion of a protein is fused to a protein having function, the fusion product could have a different function, lose function or retain function, which indicates that there is a great deal of unpredictability. It is well established in the prior art that a single amino acid change can affect the protein structure/function relationship. Thus, the instant specification needs to provide the appropriate method steps and

adequate written description to demonstrate possession of the fragments having the characteristics as claimed and possession of the soluble protein domain from the methods claimed.

This response is deemed sufficient to address the issues raised regarding the written description rejection. As the enablement rejection has been withdrawn applicant's comments on pages 10-13 are moot and will not be addressed.

With regard to the rejection under 35 U.S.C. 112, second paragraph, applicant on page 13 indicate that the response to the rejection under 112, first paragraph addresses the issues raised and that the amendments to the claims obviates this ground of rejection. However, this ground of rejection remains for the reasons stated above and based on the amendments made to the claims. As applicant did not specifically address this rejection the comments in response to the statements made regarding the rejection under 35 U.S.C. 112, first paragraph are deemed sufficient.

Note that the art rejections under 35 U.S.C. 103(a) remains. Applicant's statements have been considered but were not persuasive. Applicant state on page 13 that claims 4 and 11 although rejected over Chien in view of Waldo was not reported in the original statement of the rejection. This was an oversight, however, since the text of the rejection discussed why these claims were rejected applicant understood these claims to be rejected. Appropriate correction has been made.

Applicant uses schematics illustrated on page 14 of the response to compare the claimed invention to the cited prior art, Chien. Applicant is reminded that the combined teachings of the references render the claimed invention as obvious. The schematics

provided does not accurately illustrate the claimed invention, for example applicant state that "if the protein fluoresces, the attached fragment is considered to be a soluble domain, if it does not fluoresce, it is not", because this is not the invention as claimed. Note that the claimed methods are directed to producing a soluble protein domain, by expressing nucleotide sequences encoding fusion proteins comprised of a fragment of a starting protein and a protein exhibiting function said starting protein having a soluble domain and synthesizing the soluble domain (see for example claim 1). The Chien reference teaches Gal4 fragmented with a restriction enzyme and the expression of a fusion protein having function and luminescent. The reference also teaches transformation of *E. coli* with the DNA. The fusion partner of the reference is lacZ which applicant admits can be used to prepare a soluble domain. Applicant then argues that Waldo although relevant to the claimed invention differs because the claimed invention provides for deletion of a cloned DNA fragment encoding a protein and expressing the fragment of the protein. However, there are no steps in the methods as claimed that recite "deletion of a cloned DNA fragment", thus applicant's argument is not persuasive, and the rejections remain.

Note the new grounds of rejection under 35 U.S.C. 103(a) over the newly submitted claims for the reasons stated above.

Conclusion

15. Applicant's amendment necessitated the new/modified ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

16. No claims are presently allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Hope A. Robinson whose telephone number is 571-272-0957. The examiner can normally be reached on Monday-Friday from 9:00 a.m. to 6:30 p.m. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon P. Weber, can be reached at (571) 272-0925.

The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Hope Robinson, MS HR

Patent Examiner

JON WEBER
SUPERVISORY PATENT EXAMINER